ANTIOXIDANT AND ANTI-CHOLINESTERASE ACTIVITIES OF *Centella asiatica* PHENOLIC EXTRACT-MEDIATED GOLD NANOPARTICLES

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DEDICATION

To Almighty Allah,

the most beneficent and the most merciful,

who is the creator of this universe and guides us to search and research

the mysteries of His creations.

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ABSTRACT

In the present study, the green synthesis and optimization of gold nanoparticles (GNPs) using *C. asiatica* phenolic extract (CAP) were reported followed by the characterization with UV-vis, FTIR, Zeta potential, FESEM, EDX and XRD analyses. Total phenolic and flavonoid contents (TPC and TFC), antioxidant and anticholinesterase (anti-ChE) activities were also tested *in vitro* and Pearson correlation analysis was performed. The GNP synthesis using CAP was successfully accomplished under optimum conditions of reactants ratio of 1:1, 8 % CAP concentration, 0.5 mM $HAuCl_4$ concentration and pH 9 at different temperatures of reaction medium (25 °C, 40 °C, 55 °C and 70 °C). The results showed that the size range of GNPs was reduced from 6-40 nm at 25 °C to 6-30 nm at 40 °C and 55 °C while the sphericity of GNPs increased and the surface plasmon resonance (SPR) band became narrow. Although all GNP samples showed good antioxidant and anti-ChE activities (% I), the highest activity was recorded for the GNPs synthesized at 55 °C, that is, 69.06 % and 76.72 % for ABTS and DPPH, and 71.71 % and 69.88 % for AChE and BChE, respectively, at the highest concentration of 500 µL sample. However, the maximum % I for ABTS and DPPH scavenging (79.76±1.01 and 75.51±1.54, respectively) was shown by ascorbic acid, and for AChE and BChE inhibition (75.18±2.29 and 79.94±1.11, respectively) by galanthamine. Pearson correlation analyses revealed a strong positive correlation between antioxidant activity and phenolic content as well as between anti-ChE and antioxidant activities for all GNP samples. The GNPs did not possess a significant cytotoxicity as shown by 20% mortality in brine shrimp lethality assay. The GNPs were haemocompatible as they induced 0.92 % haemolysis at the highest concentration (500 µL) in haemolysis assay compared to 99 % haemolysis by positive control. In conclusion, the results of this study show that CAP-GNPs possess good antioxidant and anticholinesterase activities, in addition to being non-cytotoxic and non-haemolytic, may be an option to further explore their therapeutic potential as antioxidant and cholinesterase inhibitors.

ABSTRAK

Dalam kajian ini, sintesis hijau dan pengoptimuman nanopartikel emas (GNP) menggunakan ekstrak fenolik *C. asiatica* (CAP) diikuti dengan pencirian melalui analisis UV-vis, FTIR, potensi Zeta, FESEM, EDX dan analisis XRD telah dijalankan. Jumlah kandungan fenol dan flavonoid (TPC dan TFC), aktiviti antioksidan dan antikolinesterase (anti-ChE) juga diuji dalam analisis in-vitro dan kolerasi Pearson turut dilakukan. Sintesis GNP menggunakan CAP berjaya dicapai di bawah keadaan tindak balas optimum pada nisbah 1:1, 8 % kepekatan CAP, kepekatan $HAuCl_4$ 0.5 mM dan pH 9 pada suhu yang berbeza (25 ℃, 40 ℃, 55 ℃ dan 70 ℃) dalam tindak balas sederhana. Keputusan menunjukkan bahawa julat saiz GNP berkurang dari 6-40 nm pada 25 ℃ kepada 6-30 nm pada 40 ℃ dan 55 ℃, sferisiti GNPs pula meningkat dan jalur permukaan resonans plasmon menjadi sempit. Walaupun semua sampel GNP menunjukkan aktiviti antioksida dan anti-ChE yang baik (% I), aktiviti tertinggi dicatatkan untuk GNP yang disintesis pada suhu 55 ℃, untuk ABTS dan DPPH masing-masing mencatat 69.06 % dan 76.72 %, manakala untuk AChE dan BChE mencatat 71.71 % dan 69.88 %. Walau bagaimanapun, % I maksimum untuk ABTS dan DPPH (79.76±1.01 dan 75.51±1.54) masing-masing ditunjukkan oleh asid askorbik, dan untuk perencatan AChE dan BChE (75.18±2.29 dan 79.94±1.11) oleh galanthamine. Analisis korelasi Pearson menunjukkan korelasi positif yang kuat antara aktiviti antioksidan dan kandungan fenolik serta aktiviti anti-ChE dan antioksidan untuk semua sampel GNP. GNP tidak mempunyai sitotoksisiti yang ketara di mana keputusan hayat mortaliti kurang menunjukkan 20 % dalam ujian kematian udang garam. Bagi ujian hemolisis, GNP didapati sesuai di dalam darah kerana nilai hemolisis adalah 0.92 % pada kepekatan 500 µL berbanding dengan nilai hemolisis setinggi 99 % bagi kawalan positif. Kesimpulannya, hasil kajian ini menunjukkan bahawa CAP-GNP mempunyai aktiviti antioksidan dan antikolinesterase yang baik, tambahan pula ia bukan sitotoksik dan bukan haemolitik, serta mempunyai potensi terapeutik sebagai perencat antioksida dan antikolinesterase.

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LIST OF SYMBOLS AND ABBREVIATIONS

α	-	Alpha
Fl-Oº	-	Aroxyl radical
β	-	Beta
℃	-	Degree Celsius
Rº	-	Free radical
γ	-	Gamma
λ	-	Lambda
µL	-	Microliter
µM	-	Micromole
% I	-	Percent inhibition
τ	-	Tau
θ	-	Theta
ζ	-	Zeta
Aβ	-	Amyloid beta
ABTS	-	2,2′-azino-di-(3-ethylbenzthiazoline sulfonic acid)
ACh	-	Acetylcholine
AChE	-	Acetylcholinesterase
AD	-	Alzheimer’s disease
ADDL	-	Amyloid derived diffusible ligands
Ag	-	Silver
$AgCl_4$	-	Silver chloride
AgNP	-	Silver nanoparticle
ApoE	-	Apolipoprotein E
APP	-	Amyloid precursor protein
Au	-	Gold
AuNP	-	Gold nanoparticle
BACE1	-	β-site amyloid precursor protein cleaving enzyme 1

BBB	-	Blood-brain barrier
BCh	-	Butyrylcholine
BChE	-	Butyrylcholinesterase
BHA	-	Betahydroxyanisole
BHT	-	Betahdroxytoluene
BSLA	-	Brine shrimp lethality assay
C	-	Carbon
C=O	-	Carbonyl
CA	-	*Centella asiatica*
Ca	-	Calcium
CAP	-	*Centella asiatica* phenolic extract
CAT	-	Catalase
CdNP	-	Cadmium nanoparticle
CdS	-	Cadmium sulfide
Ce	-	Cerium
CeNP	-	Cerium nanoparticle
ChAT	-	Choline acetyltransferase
ChE	-	Cholinesterase
ChEI	-	Cholinesterase inhibitor
ChT1	-	Choline transporter
CNS	-	Central nervous system
CQAs	-	Dicaffeoylquinic acids
CSF	-	Cerebrospinal fluid
Cu	-	Copper
DDS	-	Drug delivery system
DMY	-	Dihydromyricetin
DNA	-	Deoxyribonucleic acid
DPPH	-	2,2-diphenyl-1-picrylhydrazyl
DTNB	-	5,5′-Dithiobis [2-nitrobenzoic acid]
EDL	-	Electrostatic double layer
EDX	-	Energy dispersive X-ray spectroscopy
EGCG	-	Epigallocatechin gallate
FDA	-	Food and drug administration
Fe	-	Iron

FESEM	-	Field emission scanning electron microscope
FL-OH	-	Flavonoid
FTC	-	Ferric thiocyanate
FTIR	-	Fourier transform infra-red spectroscopy
$GABA_A$	-	Adrenergic γ-amminobutyric acid
GAE	-	Gallic acid equivalent
GNP	-	Gold nanoparticle
GPx	-	Glutathione peroxidase
h	-	Hour
$HAuCl_4$	-	Gold chloride
HCl	-	Hydrochloric acid
HFD	-	High fat diet
H_2O_2	-	Hydrogen peroxide
Hsp	-	Heat shock protein
IC_{50}	-	Half maximal inhibitory concentration
ICV	-	Intracerebroventricular
LPO	-	Lipid peroxidation
LTP	-	Long-term potentiation
MDA	-	Malondialdehyde
min	-	Minute
mL	-	Milliliter
mM	-	Millimole
Mn	-	Manganese
MNP	-	Metal nanoparticle
MRI	-	Magnetic resonance imaging
MSG	-	Monosodium glutamate
mV	-	Millivolt
NaCl	-	Sodium chloride
NaOH	-	Sodium hydroxide
Ni	-	Nickel
NMDA	-	N-methyl-D-aspartate
NP	-	Nanoparticle
O_2	-	Oxygen
$O_2^{\bullet-}$	-	Superoxide radical

OH	-	Hydroxyl group
PAC	-	Proanthocyanidin
PBS	-	Phosphate buffered saline
PCO	-	Protein carbonyl
PECAM-1	-	Platelet endothelial cell adhesion molecule-1
PGC-1α	-	Peroxisome proliferator activated receptor-gamma co-activator-1α
PMN	-	Phenolics-mediated nanoparticle
ppm	-	Parts per million
Pt	-	Platinum
PTZ	-	Pentylenetetrazole
R^2	-	Coefficient of determination
RBC	-	Red blood cell
RE	-	Rutin equivalents
ROS	-	Reactive oxygen species
rpm	-	Revolutions per minute
Se	-	Selenium
sec	-	Second
SERS	-	Surface enhanced Raman scattering
Sirt1	-	Silent information regulator 2 family of protein 1
SOD	-	Superoxide dismutase
SPR	-	Surface plasmon resonance
STZ	-	Streptozotocin
TBA	-	Thiobarbituric acid
TBARS	-	Thiobarbturic acid reactive substance
TFC	-	Total flavonoids content
TPC	-	Total phenolics content
Ti	-	Titanium
UTHM	-	University Tun Hussein Onn Malaysia
UV-vis	-	Ultraviolet-visible
VAChT	-	Vesicular acetylcholine transporter
vdW	-	van der Waals forces
XRD	-	X-ray diffraction
Zn	-	Zinc

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LIST OF PUBLICATIONS

1. **Muhammad Sohail Latif,** Faridah Kormin, Mohd Kamarulzaki Mustafa, Ida Idayu Muhamad, Muhammad Khan, Sameera Abbas, Muhammad Ihsan Ghazali, Nor Shafawati Shafie, Mohd Fadzelly Abu Bakar, Siti Fatimah Sabran, Siti Fatimah Zahrah Mohamad Fuzi. (2018). Effect of temperature on the synthesis of *Centella asiatica* flavonoids extract-mediated gold nanoparticles: UV-visible spectra analyses. *AIP Conference Proceedings*. 2018. AIP Publishing. (Scopus indexed).
2. **Muhammad Sohail Latif**, Sameera Abbas, Faridah Kormin, Mohd. Kamarulzaki Mustafa. (2019). Green synthesis of plant-mediated metal nanoparticles: The role of polyphenols. *Asian Journal of Pharmaceutical and Clinical Research* (Scopus). Accepted for publication in vol. 12, issue 7, July, 2019.

Latest submission

1. Faridah Kormin, **Muhammad Sohail Latif,** Sameera Abbas, Ida Idayu Muhamad, Muhammad Khan, Muhammad Ihsan Ghazali, Nor Shafawati Shafie. (2018). Antioxidant and antiacetylcholinesterase activities of *Centella asiatica* for the treatment of Alzheimer's disease. *South African Journal of Botany* (ISI/Scopus indexed). Decision pending.
2. **Muhammad Sohail Latif**, Faridah Kormin, Sameera Abbas, Mohd. Kamarulzaki Mustafa, Muhammad Khan, Ida Idayu Muhamad. (2019). Antioxidant and anticholinesterase activities of *Centella asiatica* phenolics extract-mediated gold nanoparticles. *Journal of Drug Delivery Science and Technology* (ISI/Scopus indexed). Under review.

Conferences

1. **Latif, M. S.,** Kormin, F, Mustafa, M. K., Mohamad, I. I., Khan, M., Abbas, S., Ghazali, M. I., Shafie, N. S., Sabran, S. F., Zahrah, S. F., & Fuzi, Z. M. (2018). Effect of temperature on the synthesis of *Centella asiatica* flavonoids extract-

mediated gold nanoparticles: UV-vis spectra analyses. International conference on applied science & technology, 2018 (ICAST 2018) from 10th-12th April 2018 at Sunway Hotel, Penang, Malaysia. (Scopus indexed).

2. **Latif, M.S.,** Kormin, F, Mustafa, M.K., Mohamad, I.I., Khan, M., Abbas, S., Ghazali, M.I., Shafie, N.S., Sabran, S.F., Zahrah, S.F., & Fuzi, S.F.Z.M. (2018). Green synthesis of *Centella asiatica* (pegaga) flavonoids extract-mediated gold nanoparticles. International conference of chemical engineering and industrial biotechnology 2018 (ICCEIB-2018) from 1st -2nd August 2018 at Seri Pacific Hotel, Kuala Lumpur, Malaysia.

CHAPTER 1

INTRODUCTION

1.1 Background of study

In recent years, considerable efforts have been put into the use and application of nanotechnology for achieving the goal of effective drug delivery into the brain for neurological disorders (Saeedi *et al.*, 2019). In this context, the nanoparticles (NPs) have been described as an effective carrier for drug delivery to the target tissue and they have emerged as valuable tools in imaging, diagnosis and drug delivery (Rizvi & Saleh, 2018; Saraiva *et al.*, 2016).

Gold NPs (GNPs)-mediated therapeutic drug development is a promising area of research. Although GNPs were proved as the inhibitors of amyloid beta (Aβ) aggregation, the lack of specificity is an issue. However, there is convincing evidence on the use of GNPs to overcome the shortcoming posed by the blood-brain barrier (BBB) (Fonseca-Santos *et al.*, 2015; Karthivashan *et al.*, 2018). The degradation of Aβ fibrils and plaques has been reported as a treatment approach for Alzheimer's disease (AD).

The largest group of secondary metabolites in plants is constituted by the phenolic compounds including the simple ones with only one aromatic ring such as catechol and gallic acid, and the complex polymers like lignins and tannins (Altemimi *et al*., 2017). The phenolic compounds play a defensive role in the prevention of infections along with ameliorating the oxidative stress in case of injury (Setkovis et al., 2007). Various researches have indicated that phenolic compounds possess significant antioxidant activity (Cory *et al.*, 2018). It is reported that the phenolic compounds scavenge the free radicals by virtue of their hydroxyl groups or conjugated ring structures (Mathew *et al.*, 2015).

Polyphenols found in medicinal plants are reported as a diverse group of bioactive compounds with significant antioxidant activities. It was inferred that the flavonoids constitute the main phenolic compounds that confer the antioxidant properties to plant extracts (Tungmunnithum *et al.*, 2018). Many phenolic compounds including a variety of flavonoids have also been reported for their neuroprotective activity. For instance, various phenolic compounds have been reported to have anxiolytic and sedative effects in animal model studies by direct binding to adrenergic γ-amminobutyric acid ($GABA_A$) receptors, in a similar pattern as found with a tri-substituted benzoflavone moiety from *Passiflora incarnata* (Aman *et al.*, 2016; Dhawan *et al.*, 2004) and 6-hydroxyflavone (Ren *et al.*, 2010). The inhibition of acetylcholinesterase (AChE) is considered as an effective therapeutic strategy for different types of dementia including AD. A variety of plant species around the globe have been screened and reported for anti-ChE activity (Mathew & Subramanian, 2014).

Alzheimer's disease is the most common worldwide dementia disorder of old age that is still incurable even after more than a hundred years of its discovery (Franceschi *et al.*, 2018). The pathogenesis of AD has been linked with various factors such as Aβ, neurofibrillary tangles and synaptic loss in the brain especially in response to the decreased levels of neurotransmitters, acetylcholine (ACh) and butyrylcholine (BCh), and the degeneration of cholinergic neurons in the cortex and hippocampus of the brain (Sanabria-Castro *et al.*, 2017; Şenol *et al.*, 2010). The AChE and butyrylcholinesterase (BChE) are responsible for the release of ACh and BCh, respectively, at the nerve endings in the cholinergic neurons. The termination of a nerve impulse at the cholinergic synapses is carried out by the rapid hydrolysis of ACh and BCh by AChE and BChE, respectively. As the AD patients are deficient in ACh and BCh, it is imperative to raise the levels of ACh and BCh (Orhan, 2012; Reale *et al.*, 2018).

Moreover, age-related increase in oxidative stress has been strongly linked to the onset of AD. Several studies performed on AD patients reported an increasingly rapid rate of oxidative stress in the affected brains (Mecocci *et al.*, 2018) which led to the current interest in oxidative stress hypothesis to decipher the molecular basis of AD (Christen, 2000; Wojsiat *et al.*, 2018). Oxidative stress is a condition in which there is a production of reactive oxygen species (ROS) beyond the control of the

antioxidant defence system. Also, the accumulation of oxidized and damaged macromolecules due to their inefficient removal and renewal lead to oxidative stress. Although, different sources of ROS have been suggested, the active redox metals such as Fe^{2+} and Cu^{2+}, and Aβ protein ranked among the top two most common sources (Cheignon *et al.*, 2018; Di Meo *et al.*, 2016; Smith *et al.*, 2010).

The accumulation of Aβ protein in the brain leads to the generation of hydrogen peroxide (H_2O_2) depending on the presence of O_2 whereby the regulation of overall catalytic reaction is done by Fe^{2+} and Cu^{2+} (Cheignon *et al.*, 2018). A deficiency or functional loss of antioxidant enzymes like superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT), as well as the non-enzymatic antioxidant factors, as reflected by a decrease in their specific activity, has been linked with AD (Tramutola *et al.*, 2017). As a consequence of the oxidative stress, the damages occur to the cellular functions and viability in response to the ROS led damages to the cellular membranes including the intracellular content (Padurariu *et al.*, 2013). On the basis of this hypothesis, there is an overwhelming interest in the study of antioxidants such as flavonoids for the treatment of AD (Bulboaca *et al.*, 2017).

The effective treatment to delay the onset or stop the progression of AD is still lacking due to the challenges posed by the unknown aetiology of the onset of AD and a significant hindrance to brain drug delivery by the BBB. Currently available anti-AD medicines either do not stop the progressive AD pathology or are incapable of reversing the phases of disease to restore the brain function to normal (Hane *et al.*, 2017; Khoury *et al.*, 2017). Although the pathogenesis of AD has been explained by many hypotheses including Aβ hypothesis, cholinergic hypothesis, metal hypothesis, oxidative stress hypothesis, tau hypothesis, etc. (Cubinkova *et al.*, 2018), it cannot be comprehensively explained by a single hypothesis. Therefore, the current treatment regimen for AD is only focused on symptomatic amelioration. So, it is imperative to focus on new drug discovery with efficient drug delivery and effective release into the brain for the successful treatment of AD. As for the drug discovery, phytochemical screening and characterization of plants traditionally used for the treatment of AD appear to be promising which have explored many phytochemicals as therapeutic agents for AD (Atanasov *et al.*, 2015; D'Onofrio *et al.*, 2017). In this connection, nanotechnology offers two-fold benefits related to the therapeutic potential of drugs, in that it may hide the limiting properties of potential drug molecules thereby

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